Hepatic Arterial Infusion of Doxorubicin-Loaded Microsphere for Treatment of Hepatocellular Cancer: A Multi-Institutional Registry

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BACKGROUND: Hepatic intra-arterial therapy for unresectable hepatocellular cancer (HCC) has been shown to improve overall survival, but can have significant toxicity. A recent prospective randomized controlled trial demonstrated superior response rates and significantly less morbidity and doxorubicin-related adverse events with drug-eluting beads with doxorubicin (DEBDOX) compared with conventional chemoembolization. The aim of this study was to confirm the efficacy of DEBDOX for the treatment of unresectable HCC.

STUDY DESIGN: This open-label, multicenter, multinational single-arm study included 118 intermediate-staged HCC patients who were not candidates for transplantation or resection. Patients received DEBDOX at each treatment. Complications and response rates to treatment were analyzed.

RESULTS: There were 118 patients who received a total of 186 DEBDOX treatments with a median total treatment dose of 75 mg (range 38 to 150 mg), and median overall total hepatic exposure of 150 mg (range 150 to 600 mg). Five lesions were targeted, with a median size of 5.3 cm (range 1.0 to 16.9 cm). Severe adverse events related to liver dysfunction were seen after 4% of treatments. Overall survival was a median of 14.2 months (range 5 to 30 months), with progression-free survival of 13 months and hepatic-specific progression-free survival of 16 months. Okuda class less than 1 at time of treatment, reduction of alpha-fetoprotein of 1,000 ng/mL at the first post-treatment evaluation, delivery of more than 200 mg doxorubicin, and less than 25% liver involvement were all predictors of favorable overall survival assessed by multivariable analyses.

CONCLUSIONS: Hepatic intra-arterial injection of DEBDOX is safe and effective in the treatment of HCC, as demonstrated by a minimal complication rate and robust and durable tumor response. (J Am Coll Surg 2011;213:493–500. © 2011 by the American College of Surgeons)

The prognosis of patients with unresectable HCC who receive no treatment is poor, with median survival of less than 1 year.[1] Survival rates of untreated patients, randomly assigned to the control arm in 25 randomized controlled trials, ranged from 10% to 72% at 1 year, and from 8% to 50% at 2 years. Similarly, untreated patients with intermediate-stage HCC have a median survival of approximately 16 months. Because treatment options for these patients are currently so limited, any treatment that can improve survival and maintain quality of life with few severe adverse events is beneficial.

Hepatic arterial chemoembolization, or transarterial chemoembolization (TACE), has been shown in randomized controlled trials to improve median survival in intermediate-stage patients to between 19 and 20 months,[1] so is considered a first-line noncurative therapy for these patients.[2] However, TACE has been plagued by a number of problems, including a lack of standardized treatment, with variations in chemotherapeutics used, dosage of chemotherapy and type of embolic agents used, and even the number of treatments given.[3,4] This lack of standardization has led to a wide range of results and toxicity, and no clear

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Abbreviations and Acronyms

AFP = alpha feto-protein
DEBDOX = drug-eluting beads with doxorubicin
HCC = hepatocellular cancer
HR = hazard ratio
RECIST = Response Evaluation Criteria in Solid Tumors
TACE = transarterial chemoembolization
TAE = transarterial embolization

way to evaluate results from across countries or even between institutions.

A variant of the conventional TACE treatment was recently reported using a drug-eluting bead with a slow continuous release of doxorubicin.[5,6] Early phase 1 and nonrandomized phase 2 studies have confirmed the ability of this device to deliver a local, controlled, sustained dose of doxorubicin to the tumors, with minimal systemic doxorubicin exposure.[6] A recently completed randomized phase 2 study demonstrated that these drug-eluting doxorubicin beads had superior response rates when compared with conventional TACE in advanced HCC and significantly fewer overall adverse events, including doxorubicin-related side effects.[7]

Therefore, the hypothesis for this study was that similar response rates and similar safety results could be achieved using a drug-eluting bead loaded with doxorubicin when used in treating intermediate-stage HCC patients. The goal of this evaluation was to gain a better understanding of the uses of this device in intermediate-stage HCC and just as importantly, to confirm the efficacy of drug-eluting beads with doxorubicin (DEBDOX) treatment without the complications that earlier users of this device saw in the treatment of HCC. The primary endpoints for this study were 12-month response rate and overall survival in the management of intermediate-stage HCC.

METHODS

Written informed consent was obtained from each patient included in the study, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by each institutional investigational review board. This prospective multiinstitutional open, noncontrolled, repeat-treatment registry of 118 patients undergoing 186 treatments for HCC was evaluated from January 2007 to October 2009. The registry (www.ulbeadregistry.com) satisfies the strict criteria for critically appraising the quality of a registry study, including a well described patient population, ability to generate hypotheses and answer questions, high quality data, good quality control, independent assessment of outcomes, good clinically relevant follow-up with minimal loss of patients to follow-up, and comparable patient evaluation across all participating institutions.[7,8]

Patients aged 18 years or older with HCC unsuitable for resection or percutaneous ablation, (Barcelona Liver Cancer Stage A/B), without portal invasion or extrahepatic spread, were eligible for the study. Eligibility criteria also included no previous chemotherapy, radiotherapy, or transarterial embolization (TAE) (with or without chemotherapy); a confirmed diagnosis of HCC according to the European Association for the Study of the Liver (EASL), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and preserved liver function (Child-Pugh Class A or B). Patients were excluded if they had another primary tumor, advanced liver disease (defined as bilirubin levels >3 mg/dL, aspartate aminotransferase or alanine aminotransferase > 5 times the upper limit of normal or >250 U/L), advanced tumoral disease (vascular invasion or extrahepatic spread, or diffuse HCC [defined as >50% liver involvement]), or contraindications for doxorubicin administration. Standard pretherapy evaluation of patients with HCC included at least a 3-phase CT of the abdomen and pelvis or a dynamic MRI, depending on the institution and the availability of the technology for use. A target lesion was defined as any viable HCC at least 1 cm in diameter and up to 5 maximum target lesions per whole liver.

Patients were assessed for 30 days after each treatment for any treatment-related adverse experiences, and monitored for 2 years to assess survival. All adverse events were recorded using the standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0. Follow-up assessments included a tri-phase CT scan of the liver within at least 2 months of completion of treatment, with evaluation of the enhancement pattern of the target lesion and tumor response rates measured according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[9]

Image-guided infusion technique

Diagnostic angiography was performed by an interventional radiologist and consisted of selective celiac and superior mesenteric arteriogram to evaluate the hepatic arterial anatomy. For tumors near the periphery of the liver, evaluation of potential extrahepatic supply to the tumors such as the inferior phrenic, gastroepiploic, and internal mammary arteries was performed. Once the degree of hepatic tumor perfusion was evaluated, the next step was to limit any type of extrahepatic perfusion of the chemotherapeutic treatment. The most common branches that will lead to extrahepatic disposition of treatment are the right

gastric and the gastroduodenal arteries, which are either controlled before infusion using coil embolization or distal catheter placement. In addition, particular attention is paid to identification of the cystic artery to ensure that the catheter tip is past this point. This avoids extrahepatic infusion of embolic material into the gallbladder and maximizes therapy control.[10]

In addition, defining the amount of liver disease was integral to determining both the number of treatments and the type of catheter position and therapy that would be performed. For patients with fewer than 4 defined lesions of <25% overall liver tumor burden, a treatment cycle was planned for a minimum of 2 dosing schedules of DEBDOX (100 mg minimum to 150 mg maximum) loaded in 2 bead vials of 100 to 300 microns, 300 to 500 microns, or 500 to 700 microns every 4 to 8 weeks. Toxicity was followed in these patients and the interval between treatments was extended if toxicity was determined. Patients originally followed a plan of either 2 or 3 treatment cycles, based on the extent of liver involvement, with a repeat CT scan every 3 months from the first treatment cycle to evaluate response as well as planned retreatment.

For patients with bilobar disease or 26% to 50% liver tumor burden, a planned minimum of 4 treatments (100 to 150 mg each treatment, depending on the extent of tumor burden and the extent of hepatic parenchymal reserve) were loaded into 2 bead vials similar in size to those described above. The plan included at least 2 treatments per lobe every 3 to 4 weeks depending on toxicity, also as above. These patients also had a planned repeat CT scan 3 months from the first dose to evaluate tumor response. For example, if patients presented with bilobar disease, they would receive a first bead treatment to the right lobe, then 3 weeks later, a second bead treatment to the left lobe, then 3 weeks later, a third bead treatment to the right lobe, and then again 3 weeks later to the left lobe. If, at each treatment cycle, the treating physician reached complete stasis or demonstrated a complete response on follow-up CT scan, additional treatment would not be performed. Image-guided precision chemoembolization and periprocedural medications including pain medications, antibiotic prophylaxis, and corticosteroids and proton pump inhibitors were all given at the physician's discretion.

Drug preparation

All bead therapies were performed with the DC/LC bead microsphere (Drug-Eluting Bead (DEB); Biocompatibles UK). The saline suspension in the DC/LC bead microsphere was removed and the beads were mixed with doxorubicin solution at a dose of 75 mg per 2 mL at least 4 hours before the procedure depending on the dose that was planned to be delivered. The mixing of DEBDOX was performed with nonionic contrast (approximately 50/50 dilution) before injection. The minimum recommended volume of loaded bead to contrast mixture is approximately 10.0 mL to ensure smooth catheter delivery. After appropriate mixing and removal of the uneluted supernatant, a microcatheter is then placed intra-arterially. Placement is based on the extent of liver disease, as described earlier. For a finite number of lesions, the microcatheter is placed according to tumor size and location for the first bead vial (100 to 300 microns) initial infusion. The microcatheter is then pulled back to provide a lobar infusion for the second bead vial infusion (size based on physician discretion). For diffuse disease, a lobar infusion is placed into either the right or left artery, with microcatheter placement again depending on the bulk of disease. Any of the 3 bead sizes can be used for these infusions, according to physician evaluation. DEBDOX is injected slowly to avoid reflux of embolic material.

Data analysis

Data were censored at the last recorded patient contact if either endpoint (death or 12-month follow-up) was not reached. Recurrence was also evaluated using CT scan. A recurrence was defined as a reoccurrence of viable tumor by radiologic CT criteria of a vascular mass. An intralobar recurrence was defined as a new viable lesion in the lobe that was previously treated. A nonlobar recurrence was defined as a new viable lesion in the contralateral lobe that had not been treated. In the event of subsequent hepatic therapy for recurrence of disease, only the first procedure was used for the purposes of this study. Chi-square, Student's *t*-test, and Mann-Whitney's U-test for nominal, continuous, and ordinal variables were used to evaluate the association of independent variables, defined as age of patient, extent of disease, serum blood work, size of beads, dosage of doxorubicin, degree of stasis, extent of liver function, pretreatment comorbidities, technical success of treatment, and complications. Proportional hazard analysis was performed on all variables found significant by univariate analysis. Differences of $p < 0.05$ were considered significant. The proportional hazard analysis was run for all significant variables and not for each variable separately. Hazard ratios with 95% confidence intervals were calculated as a measure of association. Differences of $p < 0.05$ were considered significant. Statistical analysis was performed using JMP software (JMP; SAS Institute Inc).

RESULTS

A total of 118 patients were included in this evaluation. Median age at diagnosis of HCC was 68 years (range 35 to 88 years). The patients presented with variable past medical

Table 1. Clinical Characteristics of Intermediate HCC Treated with DEBDOX

Characteristic	n (total n=118)
Age, median, y (range)	68 (35–88)
Sex (M/F)	75/25
Medical history	
Cardiac, n (%)	20 (17)
Vascular, n (%)	6 (5)
Pulmonary, n (%)	17 (14)
Diabetes, n (%)	33 (28)
Insulin	18 (55)
Noninsulin	15 (45)
Alcohol use, n (%)	30 (25)
Tobacco use, n (%)	33 (28)
Median packs, n (range)	60 (8–350)
Hepatitis, n (%)	83 (70)
Hepatitis B	10 (12)
Hepatitis C	13 (16)
Alcohol	4 (5)
Hypertension, n (%)	49 (42)
Prior cholecystectomy, n (%)	22 (19)
Alpha-fetoprotein, ng/mL (median, range)	23 (1–252,000)
Child Pugh status: cirrhosis, n (%)	
A	83 (72)
B	32 (28)
Okuda class, n (%)	
1	98 (83)
2	20 (17)
3	0
Extent of liver lesions, n (%)	
Distinct number	94 (84)
Numerous	18 (16)
Liver involvement	
<25%, n (%)	75 (75)
26%–50%, n (%)	24 (25)
Liver tumors, median, n (range)	2 (1–25)
1, %	45
2, %	15
≥3, %	40
Sum of target lesion(s) size, median, cm (range)	5.3 (1–16.9)
Lesion location, n (%)	
Segments 2–3	5 (4)
Segments 2–4	10 (9)
Segments 4–8	9 (8)
Segments 5–8	41 (35)
Other	51 (44)

DEBDOX, drug-eluting beads with doxorubicin; HCC, hepatocellular carcinoma.

history (Table 1). A minority were current or past smokers (n = 33 of 118, 28%), with a similar distribution of current or past alcohol use (30 of 118, 25%) There was an even distribution of patients with hepatitis B (14 of 118, 12%) and hepatitis C (19 of 118, 16%), with the cause of the underlying cirrhosis being idiopathic in 45% (53 of 118) of the patients treated. All patients had cirrhosis of some form, either known or of idiopathic nature. A minority of patients had undergone previous cholecystectomy (22 of 118, 19%). A majority of patients were Eastern Cooperative Oncology Group (ECOG) grade 0 to 1 (107 of 118, 91%), Child-Pugh A (85 of 118, 72%), and Okuda class 1 (98 of 118, 83%).

The predominant liver involvement was less than 25% of the liver, with a majority of patients having at least 2 tumors (range 1 to 25 tumors). The sum of all 5 target lesions was a median of 5.3 cm (range 1.0 to 16.9 cm), with the most common locations of disease within the right lobe of the liver or in a bilobar type of distribution (Table 1).

Table 2. Bead Catheter Infusion Outcomes

Variable	Treatment/outcomes (n=186 total treatments)
Bead courses, median, n (range)	1 (1–6)
Technical success, n (%)	182 (98)
Dosage delivered, median, mg (range)	75 (38–150)
Total hepatic dose exposure, median, mg (range)	150 (150–650)
1	100 (38–150)
2	150 (100–300)
3	175 (150–450
>3	200 (175–650)
Bead size used, n	
100–300 microns	55
300–500 microns	84
500–700 microns	10
100–300 with 300–500 microns	25
300–500 with 500–700 microns	12
Complication, n (%)	33 (18)
Extrahepatic infusion, n (%)	4 (2)
Hematologic changes from before DEBDOX and after DEBDOX (within 30 d), median (range)	
WBC/μl	−0.21 (−9.46 to 9.2)
Hemoglobin, g/dL	0.4 (−5 to 5.8)
Bilirubin, mg/dL	0.1 (−0.4 to 8.9)

DEBDOX, drug-eluting beads with doxorubicin.

Image-guided DEBDOX therapy

Overall, 118 patients underwent 186 total treatments using DEBDOX (median of 1 bead treatment, range 1 to 6) (Table 2). The technical success rate was 98%, with 4 patients unable to undergo at least 50% of their planned dosing because of early stasis or vasospasm at the initial

Table 3. Bead Infusion-Related Morbidity

	All grades		Severe grade*	
Side effect	**n**	**%**	**n**	**%**
Nausea	6	14	1	2
Vomiting	6	14	1	2
Hypertension	1	2	1	2
Liver dysfunction/failure	4	9	2	5
Anorexia	2	5	1	2
Pain	3	7	0	0
Pancreatitis	3	7	1	2
Hematological	3	7	2	5
Bleeding	5	11	4	9
Other	11	25	0	0

Side effects: n = 44 DEBDOX treatments.
*Defined as Grade 3 or higher.
DEBDOX, drug-eluting beads with doxorubicin.

Table 4. Response Rates for all 118 Patients Evaluated

Response	**3 mo (n=118)**	**6 mo (n=114)**	**12 mo (n=112)**	**18 mo (n=106)***
Complete response, n (%)	15 (13)	12 (11)	8 (7)	3
Partial response, n (%)	48 (41)	54 (47)	32 (29)	10
Stable disease, n (%)	44 (37)	45 (39)	22 (20)	12
Progression of disease, n (%)	1 (1)	1 (1)	4 (4)	3
Not reached time point, n	0	0	40	76
Dead of disease, n	3	1	4	2
Dead of complication, n	1	1	2	0

*Percentages not included for 18-month data due to the number of patients not available for follow-up at that time point.

angiographic catheter placement. The total dose at each treatment session was a median of 75 mg (range 38 to 150 mg). The overall total hepatic exposure was a median of 150 mg (range 150 to 650 mg). As the number of bead treatments increased, the total cumulative dose of exposure increased, with a low median of 100 mg for patients undergoing only 1 bead treatment and a high median of 200 mg for patients undergoing greater than 3 bead treatments. Adverse events were seen in 18% of patients with extrahepatic infusion to the gallbladder found in 2% of the patients (Table 2). The median postprocedure recovery was 1 day, with a range of 23 hours (outpatient stay) to 12 days.

Adverse events

Bead-related morbidity was found in 44 treatment sessions, with the most common adverse events being nausea, vomiting, pain, and hepatic dysfunction directly related to bead treatments (Table 3). In 22 treatment sessions this adverse event led to a prolongation of hospitalization because of nausea (n = 5), emesis (n = 5), liver dysfunction (n = 2), pain (n = 2), bleeding (n = 4), pancreatitis (n = 2), fever (n = 1), and urinary tract infection (n = 1). Grades 3 and 4 adverse events were seen in 4% of the treatments (Table 3) and were related to liver dysfunction that required prolonged hospital stays or medical management, as well as postprocedural bleeding from varices of the esophagus, stomach, or duodenum, and occurring within 30 days of the last bead treatment. The incidence of bleeding was not directly related to DEBDOX infusion, but was within the 30-day follow-up period and was reported as such. In all cases, these represented variceal bleeding that may have been exacerbated from DEBDOX infusion, through a subsequent increase in portal hypertension post-therapy. The true etiology of this is unknown in these patients. This presentation was believed to be indirectly related to DEBDOX therapy. There were 4 (3%) patients who died within 30 days of their DEBDOX treatments related to liver dysfunction (n = 2) or gastrointestinal bleed (n = 2). DEBDOX bead size was not a predictor of adverse events in this population of HCC patients. There was an even distribution of adverse events across bead sizes as well as multiple patients receiving 2 different bead sizes at 1 treatment (Table 2).

Overall survival, progression-free survival, and tumor response

Overall response rate was evaluated after all patients had completed at least 6 months of follow-up; complete response and partial response were seen in 53% of patients at 3 months, 58% at 6 months, and 36% at 12 months, and there was a similar response rate in the subset of patients who were at 18-month evaluation (Table 4). Three of these patients were downstaged to transplantation and remain free of disease at 22, 26, and 33 months of follow-up. The overall survival was a median of 14.2 months (range 5 to 30 months), with a 75% 1-year survival rate, a progression-free survival of 13 months (range 6 to 32 months), a hepatic-specific progression-free survival of 16 months (range 9 months to not progressed), and an extrahepatic progression-free survival median of 13 months (range 2 to 19 months). In the 9 patients who had progression, 6 developed progression with new lesions in the untreated lobe and 3 patients developed progression in the lobe previously treated with DEBDOX. Univariate and multivariable analyses of predictors of overall survival found that an Okuda class < 1 at the time of treatment (hazard ratio [HR] 1.85, 95% CI 1.08 to 4), reduction of AFP of 1,000 ng/mL at the first post-treatment evaluation follow-up (HR 1.96, 95% CI 1.2 to 4.2), being able to deliver greater than 200 mg doxorubicin (HR 2.8, 95% CI 1.1 to 3.4), and extent of

Table 5. Multivariable Predictors of Overall Survival

Parameter	Hazard ratio	95% CI	p Value
CLIP	1.3	0.89–2.1	0.06
Okuda class <1	1.85	1.08–4.0	0.0001*
Bilobar disease	0.87	0.56–3.4	0.13
No. of lesions	0.78	0.65–3.9	0.1
Child-Pugh (A vs B)	0.68	0.54–4.2	0.3
Reduction in AFP >1,000 ng/mL	1.96	1.2–4.2	0.0006*
No. of bead treatments	3.03	1.02–4.5	0.05*
>200 mg delivered	2.8	1.1–3.4	0.04*
Extent of liver involved (<25%)	1.5	1.08–1.9	0.003*

*Statistically significant.
AFP, alpha-fetoprotein; CLIP, Cancer of the Liver Italian Program.

liver involvement less than 25% (HR 1.5, 95% CI 1.08 to 1.9), were all positive predictors of favorable overall survival (Table 5). The 8 patients who maintained a complete response after 12 months did have a more favorable overall survival; 3 went on to transplantation and had a median overall survival of 22 months (range 15 to 37months), but the numbers are small so were not used for multivariate analysis.

In an evaluation of the past single institutional and phase II prospective studies using this device, these results from this multi-institutional registry confirm similar response rates (Table 6)[11,12] and similar overall survival in studies that reported an overall survival endpoint.

DISCUSSION

Untreated HCC has a poor prognosis that is directly related to the degree of underlying cirrhosis and the cancer stage. At present, early detection offers the only realistic possibility of cure. Median survival is generally not more than 6 months in patients with a large tumor mass and Child Pugh class C cirrhosis.[13,14] Patients with small HCCs (< 5cm in diameter) and stable liver function have a better prognosis, with 2-year survival rates of around 56%.[14]

It is generally accepted that surgical resection, liver transplantation, and percutaneous ablation are the only potentially curative treatments for patients with early stage HCC.[15] These treatments induce complete responses in a high proportion of patients and are expected to improve survival accordingly. Particulate embolic agents have been used for more than 25 years for the treatment of abnormal bleeding and embolization before surgical removal of tumors, as well as in vascular malformations. More recently, embolization procedures have been used as primary treatments for tumors and vascular malformations.

Effective embolization of liver tumors using transarterial embolization is possible because of 3 prevailing circumstances: 1) The normal liver receives approximately 75% of its blood supply from the portal vein, and only about 25% of the blood is supplied from the hepatic artery;[16] 2) HCC tumors typically derive approximately 95% of their blood supply from the hepatic artery; and 3) current catheter technology allows superselective placement of catheters for safe and effective delivery of embolization agents to targeted hepatic tumors. Microcatheters allow relatively safe placement, even in the presence of aberrant vessels or collateral blood supply.

In attempts to improve the efficacy of transarterial embolization, chemotherapeutic agents such as doxorubicin have been mixed with iodinated oil (Lipiodol) and delivered with embolization agents in a procedure known as transarterial chemoembolization (TACE). TACE is the most widely used treatment for unresectable HCC. It involves the periodic injection of a chemotherapeutic agent, mixed with an embolic material, into selected branches of the hepatic artery feeding the target liver tumor. Embolization of the arteries allows greater concentrations of chemotherapeutic agents to accumulate within a target tumor site. It has been reported that the concentration of chemotherapy within tumor tissue can be 10 to 100 times greater after chemoembolization than after systemic chemotherapy.[17,18] Because embolization reduces arterial inflow to tumors, the chemotherapeutic agents will remain in contact with tumor cells for prolonged periods of time.[3] Ischemia-induced failure of transmembrane ion pumps in tumor cells[19] results in greater absorption of chemotherapeutic agents by the tumor cells, as well as prevention of the washout of the chemotherapy from those cells. In addition, cessation of blood flow in the area of the tumor prevents bulk-export of extracellular chemotherapeutic drug. DEBDOX beads are similar to the beads used for conventional TACE. DEBDOX are preformed, soft, deformable beads that occlude arteries for blocking the blood flow. These beads can be loaded with doxorubicin by the pharmacist before administration to the patient by the interventional radiologist. The targeted embolization of the tumors with the beads is, therefore, combined with the sustained local delivery of doxorubicin to the target lesion.

Recently completed phase I/II studies have demonstrated the use of DEBDOX in intermediate-stage HCC patients, with an exceptional safety profile and response rates observed ranging from 44% to 82%[6,11,20] (Table 6). These data were recently confirmed by publication of an international, multicenter, phase II, randomized, single-blind study comparing doxorubicin-loaded DC Bead (Biocompatibles) with conventional TACE (cTACE) in patients with unresectable intermediate-stage primary HCC (the PRECISION V study). Ninety-three patients were

Table 6. Response Rate and Overall Survival According to Criteria in HCC Treated with DEBDOX

First author, y	Criteria	Follow-up, mo	n	Overall response, n (%)	Complete response, n (%)	Partial response, n (%)	Stable disease, n (%)	Progression of disease, n (%)	N/A, n (%)
Malagari, 2008[11]	EASL	1	71	45 (63)	3 (4)	42 (59)	26 (37)	0 (0)	0 (0)
Poon, 2007[6]	EASL	1	30	21 (70)	2 (7)	19 (63)	2 (7)	7 (23)	0 (0)
Malagari, 2008[11]	EASL	4	63	53 (84)	4 (6)	49 (78)	8 (13)	2 (3)	0 (0)
Poon, 2007[6]	EASL	4	28	12 (43)	4 (14)	8 (29)	3 (11)	13 (46)	0 (0)
Malagari, 2008[11]	EASL	7	54	43 (80)	4 (7)	39 (72)	9 (17)	2 (4)	0 (0)
Varela, 2007[20]	EASL	6	27	18 (67)	7 (26)	11 (41)	1 (4)	5 (19)	3 (11)
Malagari, 2008[11]	EASL	10	8	7 (88)	2 (25)	5 (63)	1(13)	0 (0)	0 (0)
Poon, 2007[6]	RECIST	1	30	15 (50)	0 (0)	15 (50)	8 (27)	7 (23)	0 (0)
Poon, 2007[6]	RECIST	4	28	10 (36)	0 (0)	10 (36)	5 (18)	13 (46)	0 (0)
Varela, 2007[20]	RECIST	6	27	12 (44)	0 (0)	12 (44)	7 (26)	5 (19)	3 (11)
Kettenbach, 2007[12]	RECIST	6	30	12 (40)	8 (27)	4 (13)	1 (3)	12 (40)	5 (17)
Lammer et al 2010[7]	EASL	6	102	53 (52)	25 (27)	23 (25)	11 (12)	30 (32)	
This study	Mod RECIST	3	118	63 (53)	15 (13)	48 (41)	44 (37)	1 (1)	
This study	Mod RECIST	6	114	66 (58)	12 (11)	54 (47)	45 (39)	1 (1)	
This study	Mod RECIST	12	112	62 (55)	8 (7)	32 (29)	22 (20)	4 (4)	

DEBDOX, drug-eluting beads with doxorubicin; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; N/A, not applicable; RECIST, Response Evaluation Criteria in Solid Tumors.

treated in the doxorubicin-loaded DC Bead arm and 108 patients received conventional TACE. The primary endpoint, tumor response at 6 months according to the European Association for the Study of the Liver (EASL) response evaluation criteria, illustrated an objective tumor response of 51.6% in the doxorubicin-loaded DC Bead arm, comparing favorably with 43.5% in the cTACE arm. Compared with cTACE, doxorubicin-loaded DC Bead TACE was associated with improved tolerability and a statistically significant reduction in systemic side effects of doxorubicin. This reduction was particularly marked in relation to alopecia and liver dysfunction. Further analysis of data also demonstrated an increase in efficacy and maintenance of the safety benefits in patients with a less favorable prognosis. Overall, the trend for higher objective response and disease control rates in all patients and stratified subgroups is evidence that TACE with doxorubicin-loaded DC Bead is superior to cTACE in the treatment of intermediate HCC.

However, there were concerns regarding the use of this device as to whether the results obtained from the above study could be reproduced in other interventional radiology settings. Our study, involving a large multinational registry, demonstrates a similar overall response rate using DEBDOX instead of doxorubicin-loaded DC Bead at 6 months and effective overall survival, confirming the safety and efficacy of DEBDOX in management of intermediate-stage HCC. The adverse event rates and the severity of adverse events were also similar to those reported in previous studies, with the most common adverse event being liver dysfunction. Factors associated with more favorable outcomes and improved overall survival were also similar to those reported in previous studies, with Okuda class and extent of liver involvement being powerful predictors of improved outcomes.

Our study is the first to present data showing that an increase in overall chemotherapy delivered using DEBDOX (ie, greater than 200 mg) was also a predictor of improved overall survival. The ability of the patient to receive more than this cumulative dose is based on the patient's ability to undergo repeated DEBDOX treatments. The implication of these findings is that the use of smaller beads (100 to 300 microns) as well as not following first treatments with additional embolic material may be beneficial. This would enable repeated dosing regimens at 1- to 2-month intervals. This novel concept in the use of DEBDOX is preliminary, and is based on improving chemotherapy delivery and focusing less on inducing anoxia at the time of hepatic arterial therapy. Additional randomized studies will need to be performed to further validate these results. One of the inherent limitations of this study is the reduced overall survival when compared with other single institutional studies[21] or other prospective randomized control trials. This is a limitation of the data, but is also a true representation of HCC therapy. These data presented are the type of treatment that is occurring in the world, and therefore demonstrate a wide range in outcomes, related to patient selection, device technique, number of device treatments, and other factors. In addition, further limitations are the lack of standardized use of this

therapy once it was released onto the market, with the initial belief that this was the same as conventional TACE. However, further work has determined that this device is different in regard to dosing, catheter placement, embolization endpoints, type of radiologic follow-up, and repeated treatments. These data further confirm the need for both a standardized therapy with the use of this device and a prospective randomized control trial with an overall survival endpoint. Additional questions that must be answered concern the standardized technique for bilobar disease, optimal bead size, optimal catheter placement for therapy, and comparative studies to yttrium-90 therapy.

CONCLUSIONS

In conclusion, this large prospective evaluation of a novel doxorubicin drug-eluting bead has demonstrated safety and efficacy in the treatment of intermediate-stage HCC. Additional studies are needed to standardize optimal cumulative dose and bead size used based on the variations in intermediate-stage HCC patients.

Author Contributions

Study conception and design: Martin, Rustein, Enguix, Palmero, Carvalheiro, Urbano, Valdata, Kralj, Bosnjakovic, Tatum

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